



ACC.14

TCT@ACC-12 | innovation in intervention

A806

JACC April 1, 2014

Volume 63, Issue 12



Heart Failure and Cardiomyopathies

FIRST-IN-CLASS ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR LCZ696 MODULATES THE DYNAMICS OF THE RENIN CASCADE AND NATRIURETIC PEPTIDES SYSTEM WITH SIGNIFICANT REDUCTION OF ALDOSTERONE EXPOSURE

Poster Contributions

Hall C

Saturday, March 29, 2014, 3:45 p.m.-4:30 p.m.

Session Title: Heart Failure and Cardiomyopathies: Therapy II

Abstract Category: 14. Heart Failure and Cardiomyopathies: Therapy

Presentation Number: 1146-160

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Background: There is growing evidence that high aldosterone (AL) exposure is associated with reduced survival in patients with cardiovascular diseases. Further, the potent cardiorenal actions of natriuretic peptides (NP) that include vasodilatation, natriuresis and diuresis offer an innovative therapeutic option in the management of hypertension and heart failure. We report the results of a preclinical study investigating the effect of LCZ696, a novel angiotensin receptor neprilysin (NEP) inhibitor providing simultaneous neprilysin inhibition and AT1-receptor blockade, on the dynamics of the renin and NP cascades.

Methods: Eighteen healthy beagle dogs were placed on a low-salt diet to activate the renin-angiotensin system. The effect of 10 days of treatment (p.o., q.d.) with LCZ696 (15 and 45 mg/kg) was compared to placebo, valsartan (60 mg/kg) and benazepril (0.33 mg/kg), using a cross-over design. Biomarkers of the renin cascade and cGMP were measured in plasma on days 1, 5 and 10 of dosing and analyzed as a mean of the 3 days using random effect-repeated measures ANOVA.

Results: Compared to placebo, benazepril modestly reduced AL ($p=0.08$). In contrast, valsartan, LCZ696 15 and 45 mg/kg decreased AL levels to a significant extent (-23%, -45% and -43%, respectively, $p<0.05$). The greatest reductions were observed in the LCZ696 groups, where LCZ696 15 mg/kg at 2 hours reduced AL 2-fold lower than valsartan ($p<0.05$). Administration of LCZ696 at 45 mg/kg resulted in a 180% increase of cGMP relative to placebo ($p<0.0001$), which is consistent with enhanced NP action consecutive to NEP inhibition. Neither valsartan nor benazepril changed cGMP levels. In LCZ696 45 mg/kg treated dogs, an ~2.5-fold (1.8-3.7) increase from placebo was found for renin activity ($p<0.0005$), angiotensin I ($p<0.005$) and angiotensin II ($p<0.05$), reflecting a known compensatory up-regulation of the renin-angiotensin system to AT1-receptor blockade.

Conclusion: The greater reduction of AL with LCZ696 over valsartan is consistent with the simultaneous blockade of the AT1-receptor and enhancement of the NP system. These results support further development of LCZ696 for the management of cardiovascular diseases.